International Journal of Orthopaedics

Online Submissions: http://www.ghrnet.org/index./ijo/
doi:10.6051/j.issn.2311-5106.2014.01.7

Int Journal of Orthopaedics 2014 June 23 1(1): 19-24
ISSN 2311-5106

ORIGINAL ARTICLE

The Effect of Methylsulfonylmethane on Osteoarthritic Large Joints and Mobility

Thomas A Pagonis, Panagiotis A Givissis, Aristidis C Kritis, Anastasios C Christodoulou

Thomas A Pagonis, Spinal Unit, Trauma and Orthopaedic Department, The Ipswich Hospital, 106 Foundry Lane, IP4 1DJ, Ipswich, Suffolk, the United Kingdom
Panagiotis A Givissis, Anastasios C Christodoulou, 1st Orthopaedic Department of Aristotle's University, G.U.H.G.Papanikolaou, Thessaloniki, Greece
Aristidis C Kritis, Department of Physiology and Pharmacology, Lab of Physiology, Medical school Aristotle's University, Thessaloniki, Greece
Correspondence to: Thomas A Pagonis, Spinal Unit, Trauma and Orthopaedic Department, The Ipswich Hospital, 106 Foundry Lane, IP4 1DJ, Ipswich, Suffolk, the United Kingdom
Email: iatros1@yahoo.com
Telephone:+44 (0) 7896360517
Received: April 9, 2014 Revised: May 23, 2014
Accepted: May 29, 2014
Published online: June 23, 2014

ABSTRACT

AIM: Methylsulfonylmethane (MSM) is a non-pharmacologic nutrition supplement used against osteoarthritis (OA). Objective: Delineate the effect of MSM on osteoarthritic joints and mobility.

MATERIALS AND METHODS: Randomized, double-blind, placebo-controlled trial including 100 patients, with hip and/or knee OA stratified in an intervention and a placebo group. Intervention: MSM 6 gr per day or placebo for 26 weeks. Outcomes measured were the Western Ontario and McMaster University Osteoarthritis Index visual analogue scale (WOMAC), patient and physician assessments and SF-36 (overall health-related quality of life).

RESULTS: Compared to placebo the MSM group presented significant decreases in all subscales of WOMAC ($P < 0.05$) with improved performance of daily living activities on the SF-36 evaluation ($P < 0.05$). Patient and Physician assessments exhibited favorable effects on the MSM group

CONCLUSION: MSM improved all physical symptoms in the WOMAC scale during the short intervention without any adverse events.

Key words: Methylsulfonylmethane (MSM); Osteoarthritis; OA treatment; Pain relief; Knee arthritis; Arthritic pain; Complementary and alternative medicine

Pagonis TA, Givissis PK, Kritis AC, Christodoulou AC. The Effect of Methylsulfonylmethane on Osteoarthritic Large Joints and Mobility. *International Journal of Orthopaedics* 2014; 1(1): 19-24 Available from: URL: http://www.ghrnet.org/index.php/ijo/article/view/745

INTRODUCTION

Osteoarthritis (OA) derived from the Hellenic Words Osto (Bone) and Arthritis (Arthritis) is a common form of non-inflammatory degenerative arthritis causing moderate to major disability and limiting everyday activities in an ever increasing number of the elderly community[1], thus diminishing their quality of life[2]. Current trends for controlling the debilitating pain associated with OA include but are not limited to: use of analgesic drugs[3,4], surgical interventions[5], and an ever increasing inclination to employ complementary and alternative medicine (CAM)[6] treatments. Methylsulfonylmethane (MSM) is currently a non pharmaceutical dietary supplement used alone or conjugated with glucosamine and/or chondroitin sulfate[7-10] validated as a CAM treatment by the FDA in the USA.

MSM is a complex containing organic sulfur $(CH_3)_2SO_2$[11]. It is strongly affiliated to dimethyl sulfoxide or DMSO although it's chemical interaction is somewhat different[12-19]. MSM is the prime metabolite for DMSO in the human organism alongside sulfur-containing-amino acids, thus exhibiting a significant anabolic action in the process of sulfomethylation. Studies suggest that approximately 15% of orally ingested DMSO is metabolized into MSM in the human organism[20]. MSM is used by the body to maintain and repair connective tissue[21] and anecdotal evidence suggest it may exhibit some anti-inflammatory, anti-atherosclerotic and chemo-preventive properties, may inhibit prostacyclin (PGI2) synthesis, may influence eicosanoid metabolism, and improve free radical scavenging processes[22-24]. Studies performed in murine models showed that MSM had an effect in inflammatory conditions (e.g. rheumatoid arthritis, lupus)[25,26]. Up to date a single randomized controlled trial of MSM and OA has been published showing considerable decrease

in OA pain[27].

Currently there is lack of valid published clinical studies concerning MSM safety and toxicity with a handful of small animal trials reporting no adverse events, organ pathology or mortality[28]. Dosology used in these reports was four to seven times the maximum FDA approved dose and those currently used by off-the-shelf buyers. MSM is considered a "safe" dietary supplement, and is listed as such on the "Guide to Alternative Therapies for OA" of The Arthritis Foundation along with a cautionary note stating "lack of research"[29]. Although structured and valid clinical studies on the possible adverse effects are almost nonexistent, there have been unverified reports of mild adverse effects from the oral use of MSM[30] while an animal clinical study reported decreased joint degeneration[31].

The lack of significant scientific evidence in the form of solid clinical trials needs to be addressed if the promising anecdotal evidence of MSM's potency is ever to be validated and verified.

MATERIALS AND METHODS

Participants

The study was approved by the ethics committee of the medical institutions involved in the research. Written consents were obtained from all participants before initiation of the selection and allocation process. Patients affected by hip and knee OA were selected so as to better evaluate large joints that are effortlessly examined by use of simple X-rays, making our preliminary efficacy clinical research much easier. Presence of OA in other joints was not an exclusion criterion, but we were careful to monitor all patients for comorbidities in the rest of the skeleton.

Our study cohort included males and females >45 years of age diagnosed with hip or/and knee OA. Inclusion criteria for our study included: For stratification purposes we used the modified criteria of the American College of Rheumatology (ACR)[32,33] stratified into ACR functional class I, II or III[34]; categorization into Kellgrene Lawrence grades 2-3 (mild to moderate joint space narrowing with osteophytes present)[35] was radiographically confirmed (by use of A-P and L X-rays of joints involved); standard arthritis pain (present regularly most of the days) for 3 months or more; >40 mm arthritis pain rating of joint under investigation (in the 100 mm visual analogue scale or VAS); and >2 rating on the patient global assessment (GA) tool of overall arthritis disease status (Five-Point Likert scale).

Exclusion criteria included: any other type of arthritis or chronic pain syndrome; previous arthroscopic surgery or surgical intervention in the past 8 months, intra-articular corticosteroids and/or hyaluronic acid injections in the past 8 months, malignancy, narcotic pain killers use, renal or hepatic disease, body mass index (BMI) >45 kg/m^2. A washout period of 21 days was required concerning NSAID and CAM use.

Enrollment and randomization procedures. We recruited patients from the busy outpatients department (OPD) and emergency room (ER) attendants on the basis of them already fulfilling the aforementioned criteria. Initial screening was conducted in person by the author and patients were made aware of the protocol and its parameters. A more frequent OPD attendance on a scheduled and an emergency basis along with extra blood tests and radiographic control was offered free of charge to all participants as a reward bonus. Written consents were obtained from all willing participants. Patients qualifying for inclusion were assigned to either group A (intervention MSM; n=50) or group B (intervention placebo; n=50) in a 26-week randomized, double-blind, placebo-controlled trial. The allocation of patients in either group was random and was performed with the help of computer-generated random numbers. Generated numbers and subsequent patient allocation were provided by different research staff not involved in patient contact or data collection. All patients were informed to abstain from analgesics and NSAIDs but to state rescue analgesic used on intolerable pain. Unbeknownst to the patients, those using the aforementioned compounds were later excluded from the research. Weekly calls to patients were made during the 26 weeks by the researchers, follow-ups were performed on an as needed basis and a final follow up was performed after the end of week 26 for each patient separately.

MSM dosage and preparation

A daily dosage of a total of 6 gr (3gr used twice per day) of MSM powder was selected and this rational was based on FDA guidelines, prior pilot studies and common clinical and over-the-counter use of MSM. Patients were instructed to take the compound on an empty stomach, with water or juice and not too close to bedtime. Distilled MSM powder was used with an included dosimeter to guarantee a dose of 3gr which had to be diluted in 250 mL of water or juice. The purity of the used MSM compound was confirmed by the producer to be 99.9% (by use of high-resolution gas chromatography). The placebo compound was indistinguishable in all qualities when compared to the MSM and consisted solely of inert ingredients. Both the MSM compound and the placebo were certified to be free of microbiological contamination. Canisters containing MSM or placebo were identical in size, shape, color and brand but had different bar codes for identification purposes. The canisters were provided to the patients by pharmacy personnel blinded to the patients' identity so that the researchers were also blinded to the patients' group allocation.

Efficacy evaluations

The joint (or joints) indicated by the patient as the one exhibiting the worst arthritis pain (study target) was noted during the initial screening process and was later evaluated for MSM efficacy. The difficult task was to select an appropriate tool that would enable us to stratify and categorize OA pain and symptoms. Towards that goal we implemented the Western Ontario and McMaster University Osteoarthritis Index VAS (WOMAC version 3.1) that includes composite subscales on pain (five questions), stiffness (2 questions), physical function (17 questions), and cumulative total symptoms (24 questions)[36,37]. The WOMAC was scored from 0 mm to 100 mm (0=no pain, 100=worst pain), and collected at baseline and 26 weeks after that at the end of the study period.

In order to collect stratifiable data concerning quality of life we also studied the patient GA, physician GA, and SF-36 (version 2), at baseline and at 26 weeks. Both patient and physician GA were scored based on a five-point Likert scale for overall OA status (0=very well, 1=well, 2=moderate, 3=poor, 4=very poor) and response to therapy (0=excellent response, 1=good response, 2=moderate response, 3=slight response, 4=no response). We included the SF-36 as a previously applied and validated measurement tool in precedent OA efficacy studies[29-31]. SF-36 includes 36 items (questions), with responses categorized into eight domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). Scores range from 0 to 100 with higher scores representing superior health status and quality of life.

Adverse effects evaluations

Questionnaires, laboratory tests, weight alterations, BMI, and

other parameters were collected both at baseline and at 26 weeks. Laboratory tests included blood tests (complete blood counts and differential white blood cells, renal and hepatic functions), fasting lipid profile and urinalysis. Questionnaires included standard GI symptoms and adapted neurotoxic symptoms using a four-point Likert scale ranging from 0 to 3 (0=no, 1=mild, 2=moderate, 3=severe). Customizations were made on the usual neurotoxicity questionnaires used in past drug trials so that they could be easily applied in our study[41-43]. These questionnaires were used to measure: cognitive function, peripheral neurological symptoms, and associated symptoms like sleeplessness, persistent headaches and episodes of blurred vision).

Statistical analysis

Statistical analysis was performed using SPSS (version 11.0) software. The basis of our research was the cohort size that had to include enough patients to validate any results. The estimated cohort size needed for this research was calculated by using an 80% power with a two-sided (tailed) test, alpha of 0.05 to detect a 25% improvement in VAS arthritis pain score from baseline to 26 weeks in the MSM treated group. Estimated variance and power calculation were based on earlier knee OA pilot trial publications[46,47]. This process indicated that a sample size of at least 22 patients was required[44,45] to be included as an intervention group (MSM group) for our research results to have significant power. With an anticipated 10% attrition rate, we opted to select 50 patients in each group since this numbers were deemed to be more than adequate to meet sample size requirements. The measured changes from baseline to 26 weeks between groups were considered significant for Kruskal-Wallis non-parametric ANOVA p values<0.05.

RESULTS

Demographics and baseline measurements

Mean age of the MSM group patients was 61.2 years and their ACR categorization was 11.9% class I, 80.7% class II, and 7.4% in class III (Table 1). This demographic profile was comparable to the Placebo group where mean age was 60.6 years and ACR categorization was 14.3% class I, 78.8% class II, and 6.9% in class III. Average arthritis duration from the time of initial diagnosis was 9.1 and 8.6 years for the MSM and placebo groups respectively. According to WOMAC scoring, mean "Pain" level was 57.3 mm in the MSM group and 57.1 mm in the placebo group, which were comparable baseline values. The same applied to "Stiffness" with mean values of 53.6 for the MSM group and 54.0 for the placebo group, "Physical Function" with values of 54.8 and 53.2 respectively and "Total Symptoms" values of 42.5 and 42.9 at the baseline measurements.

Table 1 Demographics of patients in both groups.

	MSM	PLACEBO
Gender (%)		
Male	44.7	48.1
Female	55.3	51.9
Age (mean)	61.2 (SD=9.1)	60.6 (SD=8.2)
ACR classification (%)		
I	11.9	14.3
II	80.7	78.8
III	7.4	6.9
Kellgren – Lawrence Grade (%)		
2	63.5	64.1
3	36.5	35.9
Arthritis first diagnosed (years mean)	9.1 (SD=4.6)	8.6 (SD=5.2)
BMI (mean)	27.1	26.4

Demographic presentation of both groups.

No major differences in the baseline arthritis disease status and demographic characteristics were found between the MSM and placebo group during enrolment and at the subsequent baseline measurement. Baseline patient profiles suggested that any measured changes observed after the intervention were not associated to any variability of patients in our two study groups. Compliance with compound taking and other protocol instructions were observed in all enrolled patients by regular interviews. The compound canisters were returned to the researchers at the end of the treatment, and the number of doses still present in them were correlated to the expected usage by that specific patient. Using this method we were able to verify if the doses used by the patient correlated to a strict adherence to our protocol of use.

Efficacy results

Treatment results as measured through WOMAC are listed in Table 2. The changes at 26 weeks in the MSM group were significantly better when compared to the placebo group for all subscales (pain, stiffness, physical function and total symptoms). Changes in the Placebo group were minor at the 26 week follow-up with the difference between the two groups being statistically significant in all subscales (p<0.05). Patient and physician GA for overall OA status changes at 26 weeks in the MSM group and placebo group were statistically significant, p<0.05 (Table 2). Changes in disease status suggest a strong trend toward improvement in the MSM treatment group. The patient GA and physician GA of response to therapy also showed fair differences suggesting an improvement of the MSM group.

Scores derived from the SF-36 quality of life tool, showed significant differences in all eight domains at 26 weeks in the MSM group. Physical Functioning difference was at 18.45, p<0.05, Bodily pain difference was at 21.20, p<0.05, General health difference was at 14.45, p<0.05 and Vitality difference was at 26.45, p<0.05. In the

Table 2 WOMAC, Patient GA and Physician GA.

	MSM			PLACEBO			
WOMAC (0–100 mm VAS)	Baseline (mean and variation)	26 week follow up (mean and variation)	Change (mean)	Baseline (mean and variation)	26 week follow up (mean and variation)	Change (mean)	Differencebetween groups p value
Pain	(57.3 ± 4.2)	(36.2 ± 3.1)	- 21.1	(57.1 ± 3.8)	(53.2 ± 4.1)	- 3.9	< 0.05
Stiffness	(53.6 ± 5.6)	(32.6 ± 4.1)	- 21	(54.0 ± 5.8)	(52.1 ± 5.5)	- 1.9	< 0.05
Physical Function	(54.8 ± 3.8)	(30.1 ± 2.6)	- 24,7	(53.2 ± 4.1)	(52.6 ± 3.2)	- 0.6	< 0.05
Total Symptoms	(42.5 ± 4.1)	(26.8 ± 5.0)	- 15,7	(42.9 ± 4.9)	(40.1 ± 3.8)	- 2.8	< 0.05
Patient GA (0–4 Likert)							
Disease Status	(3.2 ± 0.2)	(2.4 ± 0.1)	- 0.8	(3.0 ± 0.1)	(2.8 ± 0.2)	- 0.2	< 0.05
Physician GA (0–4 Likert)							
Disease Status	(3.0 ± 0.2)	(2.2 ± 0.2)	- 0.8	(2.8 ± 0.2)	(3.0 ± 0.4)	- 0.2	< 0.05
Quality of life score [mean] (range)		31,21 (6 – 81)			62,40 (19 - 98)		< 0.05

Presentation of WOMAC, Patient and Physician GA scores (mean and variation) for each group, along with mean change and p values for difference between groups.Demographics of patients in both groups.

placebo group, a mean change of 10.48 was observed on the Social functioning domain, which was not statistically significant (p>0.05). No notable changes were found in the other seven domains, P>0.05. There were appreciable differences in the use of rescue analgesics; over the 26 weeks period 5 patients in the placebo group used NSAIDs compared to 2 in the MSM group.

Lab monitoring

All tests did not exhibit any abnormal alterations from baseline to 26 weeks in any of our groups. There were no major changes in the complete blood counts, differential white blood cell counts, hepatic and renal functions, lipid profiles, BMI and vitals with all values remaining comparable between the two groups. No adverse effects were observed in any of our groups.

Of the 50 patients enrolled in each group (total of 100 for both groups), 89 completed the study: 48 (96%) in the MSM group and 41 (82%) in the Placebo group (Figure 1). The majority of patient withdrawals were reportedly due to NSAID use with two cases occurring in the MSM group and five in the Placebo group respectively. This difference in withdrawal numbers also suggests a favorable effect on the MSM use. One patient in the Placebo group was lost to follow-up. Three more patients were excluded from the Placebo group due to their inability to follow the protocol and also due to reported use of narcotic analgesics and further CAM therapies.

DISCUSSION

Our clinical trial incorporated CAM treatment in the form of MSM used at a dose of 3 gr twice a day for 26 weeks. This intervention produced patient-perceived improvement present in all of the WOMAC subscales, with differences being statistically significant p<0.05 between study groups.

Our carefully formed protocol and carefully selected sample size produced two demographically comparable study groups. Patients and researchers alike were blinded to the true intervention suggesting that the sole compound affecting the arthritis status was the tested substance (MSM). The lack of improvement in the placebo group and the statistically significant differences between the two groups indicate that the effect of MSM was valid with the clinical significance of the improvement of these symptoms acting as solid proof.

The overall trend in WOMAC subscales decrease does suggest that the group using MSM was benefited by the compound while making obvious the need for further clinical evaluation before practical application. Moreover, another noteworthy finding is that all WOMAC subscales continued to decline at 26 weeks, suggesting that the full effects of MSM were not entirely expressed during the planned intervention timeframe (26 weeks); a lengthier study is needed to delineate and analyze if and when the effects of MSM would reach a pharmacological plateau, needing further treatment addition or modification. Patient and physician GA trends correlated with those observed in WOMAC subscales in the MSM group.

Our trial did not reveal any adverse events such as high blood pressure, changes in blood chemistry, increased bruising, or bleeding time. The lack of any acute and/or midterm adverse effects were thus validated but a lengthier trial that would go on for several months would be much more prone to reveal long term side effects. The inclusion of patients with different comorbidities would also ensure that the efficacy of the compound is measured on a more homogenous and real-time community simulating population.

Using our Department as an enrollment site, we increased patient pool size, variability and external validity due to the fact that we admit and treat patients from a catchment population pool of three million.

MSM is used by the body to maintain and repair connective tissue[21] and it has been suggested that it may exhibit some anti-inflammatory, anti-atherosclerotic and chemo-preventive properties, may inhibit prostacyclin (PGI2) synthesis, may influence eicosanoid metabolism, and improve free radical scavenging processes, along with a reduce in the IL-1β-induced nuclear factor-kB (NF-κB) translocation in chondrocytes[22-24].

Osteoarthritis on the other hand is a chronic rheumatoid disease mediated by metalloproteinases and inflammatory cytokines. Methylsulfonylmethane (MSM) shows promise in the treatment of inflammatory processes, but the efficacy of prolonged treatment with this substance in the management of OA has not yet been studied. MSM containing organic sulfur is strongly affiliated to dimethyl sulfoxide (or DMSO) being it's prime metabolite. This effect resembles the anabolic action of sulfur- containing-amino acids, thus exhibiting a significant effect in the process of sulfomethylation[48].

MSM is used by the body to maintain and repair connective tissue[21] and anecdotal evidence suggest it may exhibit some anti-inflammatory, anti-atherosclerotic and chemo-preventive properties, may inhibit prostacyclin (PGI2) synthesis, may influence eicosanoid metabolism, and improve free radical scavenging processes[22-24]. The strongest effect is likely the result of a number of reactions including its anti-inflammatory activity, the stimulation of the synthesis of proteoglycans and hyaluronic acid, and the decrease in catabolic activity of chondrocytes inhibiting the synthesis of proteolytic enzymes, nitric oxide, and other substances that contribute to damage cartilage matrix and cause death of articular chondrocytes. The rationale behind the use of MSM is based on the belief that osteoarthritis is associated with a local deficiency or degradation of natural substances leading to increased apoptosis. In an in vitro study, MSM reduced the IL-1β-induced nuclear factor-kB (NF-κB) translocation in chondrocytes[48-50].

Our study limitations include a statistically sound and adequate but nonetheless restricted sample size, with patients that were free of severe comorbidities and a mediocre duration of treatment (26 weeks) resulting in limitations in extrapolation to the targeted elderly population of the community, usually including an increasing number of octogenarians and nonagenarians. Nonetheless, the fact that the noticed improvement in the MSM group was detected early is a promising indication for a long term efficacy research. The need for significant funding is a strong limitation to address all the aforementioned optimum research parameters.

Our study findings are preliminary and act as a pilot suggestion for further research. No dose response directions can be determined and the need arises for further clarification of optimum dosages appropriate for treatment of OA in the broader community.

Based on our results and on older studies, future research on MSM must include larger and more varied sample sizes, long-term treatments, dose response trials and clinical studies to delineate bioactivity of MSM. MSM-drug interaction studies for safety and toxicity seem appropriate, since the target group is the elderly with significant and varied co-morbid conditions suggesting administration of many different drug compounds. Research should revolve around the anecdotal evidence of MSM's antioxidant activity which may also be extremely beneficial to the elderly population.

Our results support previous anecdotal reports that intervention with MSM on elderly patients suffering from OA is beneficial. A treatment approach based on current literature is to start off at 3 g/

day, then to increase up to 6 g/day in two divided doses. Although large, long-term dose response studies are necessary, MSM should be considered in certain OA patient populations.

Key Messages: (1) OA is a major cause of disability affecting day to day activities and quality of life; (2) The effect of a CAM therapy like MSM is favorable without showing any adverse effects; (3) The physicians counsel is paramount to the selection of an appropriate treatment.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

REFERENCES

1 Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, Heyse SP, Hirsch R, Hochberg MC, Hunder GG, Liang MH, Pillemer SR, Steen VD, Wolfe F. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998; **41**: 778-799

2 Ethgen O, Vanparijs P, Delhalle S, Rosant S, Bruyere O, Reginster JY. Social support and healthrelated quality of life in hip and knee osteoarthritis. *Qual Life Res* 2004; **13**: 321-330

3 Geba GP, Weaver AL, Polis AB, Dixon ME, Schnitzer TJ. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: a randomized trial. *JAMA* 2002; **287**: 64-71

4 Gottesdiener K, Schnitzer T, Fisher C, Bockow B, Markenson J, Ko A, DeTora L, Curtis S, Geissler L, Gertz BJ; Protocol 007 Study Group. Results of a randomized, dose-ranging trial of etoricoxib in patients with osteoarthritis. *Rheumatology (Oxford)* 2002; **41**: 1052-1061

5 Dieppe P, Basler HD, Chard J, Croft P, Dixon J, Hurley M, Lohmander S, Raspe H Knee replacement surgery for osteoarthritis: effectiveness, practice variations, indications and possible determinants of utilization. *Rheumatology (Oxford)* 1999; **38**: 73-83

6 Felson DT, Lawrence RC, Hochberg MC, McAlindon T, Dieppe PA, Minor MA, Blair SN, Berman BM, Fries JF, Weinberger M, Lorig KR, Jacobs JJ, Goldberg V. Osteoarthritis: new insights. Part 2: treatment approaches. *Ann Intern Med* 2000; **133**: 726-737

7 McAlindon TE, LaValley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and metaanalysis. *JAMA* 2000; **283**: 1469-1475

8 Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3- year, randomized, placebo-controlled, double-blind study. *Arch Intern Med* 2002; **162**: 2113-2123

9 Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, Giacovelli G, Henrotin Y, Dacre JE, Gossett C. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo- controlled clinical trial. *Lancet* 2001; **357**: 251-256

10 Morton JI, Siegel BV. Effects of oral dimethyl sulfoxide and dimethyl sulfone on murine autoimmune lymphoproliferative disease. *Proc Soc Exp Biol Med* 1986; **183**: 227-230

11 Kocsis JJ, Harkaway S, Snyder R. Biological effects of the metabolites of dimethyl sulfoxide. *Ann N Y Acad Sci* 1975; **243**: 104-109

12 Jacob SW, Appleton J. MSM-The Definitive Guide. Topanga, Freedom Press; 2003.

13 Usha PR, Naidu MUR. Randomised, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis. *Clin Drug Invest* 2004; **24(6)**: 353-363

14 Blinn CM, Biggee BA, McAlindon TE, Nuite M, Silbert JE. Sulphate and osteoarthritis: Decrease of serum sulphate levels by an additional 3-h fast and a 3-h glucose tolerance test after an overnight fast. *Ann Rheum Dis* 2006; **65**: 1223-1225

15 Georges Hareau and Philip Kocienski, "Dimethyl Sulfone" in Encyclopedia of Reagents for Organic Synthesis. *John Wiley & Sons*; 2001

16 Pearson TW, Dawson HJ, Lackey HB. Natural occurring levels of dimethyl sulfoxide in selected fruits, vegetables, grains and beverages. *J Agric Food Chem* 1981; **29**: 1019-1021

17 Murav'ev IuV, Venikova MS, Pleskovskaia GN. Effect of dimethyl sulfoxide and dimethyl sulfone on a destructive process in the joints of mice with spontaneous arthritis. *Patol Fiziol Eksp Ter* 1991; **2**: 37-39

18 Williams KIH, Burstein SH, Layne DS. Dimethyl sulfone: isolation from cows' milk. *Proc Soc Exp Biol Med* 1966; **122**: 865-866

19 Kim LS, Axelrod LJ, Howard P, Buratovich N, Waters RF. Efficacy of methylsulfonylmethane (MSM) in osteoarthritis pain of the knee: a pilot clinical trial. *Osteoarthritis Cartilage* 2006; **14**: 286-294

20 Hucker HB, Miller JK, Hochberg A, Brobyn RD, Riordan FH, Calesnick B. Studies on the absorption, excretion and metabolism of dimethylsulfoxide (DMSO) in man. *J Pharmacol Exp Ther* 1967; **155**: 309-317

21 Engelke UF, Tangerman A, Willemsen MA, Moskau D, Loss S, Mudd SH, Wevers RA. Dimethyl sulfone in human cerebrospinal fluid and blood plasma confirmed by onedimensional (1)H and two-dimensional (1)H-(13)C NMR. *NMR Biomed* 2005; **18**: 331-336

22 Ebisuzaki K. Aspirin and methylsulfonylmethane (MSM): a search for common mechanisms, with implications for cancer prevention. *Anticancer Res* 2003; **23**: 453-458

23 Alam SS, Layman DL. Dimethyl sulfoxide inhibition of prostacyclin production in cultured aortic endothelial cells. *Ann N Y Acad Sci* 1983; **411**: 318-320

24 Beilke MA, Collins-Lech C, Sohnle PG. Effects of dimethyl sulfoxide on the oxidative function of human neutrophils. *J Lab Clin Med* 1987; **110**: 91-96

25 Morton J, Moore R. Lupus nephritis and deaths are diminished in B/W mice drinking 3% water solutions of dimethyl sulfoxide (DMSO) or dimethyl sulfone (DMSO2). *J Leukoc Biol* 1986; **40**: 322

26 Hasegawa T. Suppressive effect of methylsulfonylmethane (MSM) on type II collagen-induced arthritis in DBA/1J mice. *Jpn Pharmacol Ther* 2004; **32**: 421-427

27 Usha P, Naidu M. Randomised, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis. *Clin Drug Invest* 2004; **24**: 353-363

28 Horvath K, Noker PE, Somfai-Relle S, Glavits R, Financsek I, Schauss AG. Toxicity of methylsulfonylmethane in rats. *Food Chem Toxicol* 2002; **40**: 1459-1462

29 Horstman J, Arnold W. The Arthritis Foundation's Guide to Alternative Therapies. Atlanta: *Arthritis Foundation* 1999

30 Jacob S, Appleton J. MSM The Definitive Guide. Topanga: Freedom Press 2003

31 Murav'ev Iu V, Venikova MS, Pleskovskaia GN, Riazantseva TA, Sigidin Ia A. Effect of dimethyl sulfoxide and dimethyl sulfone on a destructive process in the joints of mice with spontaneous arthritis. *Patol Fiziol Eksp Ter* 1991; 37-39

32 Bellamy N, Klestov A, Muirden K, Kuhnert P, Do KA, O'Gorman L, Martin N. Perceptual variation in categorizing individuals according to American College of Rheumatology classification criteria for hand, knee, and hip osteoarthritis (OA): observations based on an Australian Twin Registry study of OA. *J Rheumatol* 1999; **26**: 2654-2658

33 Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, Christy W, Cooke TD, Greenwald R, Hochberg M. Development of criteria for the classification and reporting of osteoarthritis.

Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986; **29**: 1039-1049
34 Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. *Arthritis Rheum* 1992; **35**: 498-502
35 Menkes CJ. Radiographic criteria for classification of osteoarthritis. *J Rheumatol Suppl* 1991; **27**: 13-15
36 Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988; **15**: 1833-1840
37 Davies GM, Watson DJ, Bellamy N. Comparison of the responsiveness and relative effect size of the western Ontario and McMaster Universities Osteoarthritis Index and the short-form Medical Outcomes Study Survey in a randomized, clinical trial of osteoarthritis patients. *Arthritis Care Res* 1999; **12**: 172-179
38 Hauser W, Zimmer C, Schiedermaier P, Grandt D. Biopsychosocial predictors of health-related quality of life in patients with chronic hepatitis C. *Psychosom Med* 2004; **66**: 954-958
39 Katz JN, Larson MG, Phillips CB, Fossel AH, Liang MH. Comparative measurement sensitivity of short and longer health status instruments. *Med Care* 1992; **30**: 917-925
40 Karlsson J, Sjogren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double- blind, parallel-design multicentre study. *Rheumatology (Oxford)* 2002; **41**: 1240-1248
41 Pace A, Bove L, Aloe A, Nardi M, Pietrangeli A, Calabresi F, P. Innocenti, B. Jandolo. Paclitaxel neurotoxicity: clinical and neurophysiological study of 23 patients. *Ital J Neurol Sci* 1997; **18**: 73-79
42 Aldenkamp AP, Baker G, Pieters MS, Schoemaker HC, Cohen AF, Schwabe S. The Neurotoxicity Scale: the validity of a patient-based scale, assessing neurotoxicity. *Epilepsy Res* 1995; **20**: 229-239
43 Aldenkamp AP, Baker GA. The Neurotoxicity Scale dII. Results of a patient-based scale assessing neurotoxicity in patients with epilepsy. *Epilepsy Res* 1997; **27**: 165-173
44 Altman DG. Practical Statistics for Medical Research. Boca Raton: CRC Press 1999
45 Altman R, Brandt K, Hochberg M, Moskowitz R, Bellamy N, Bloch DA, Buckwalter J, Dougados M, Ehrlich G, Lequesne M, Lohmander S, Murphy WA Jr, Rosario-Jansen T, Schwartz B, Trippel S. Design and conduct of clinical trials in patients with osteoarthritis: recommendations from a task force of the Osteoarthritis Research Society. Results from a workshop. *Osteoarthritis Cartilage* 1996; **4**: 217-243
46 Bellamy N, Buchanan WW, Chalmers A, Ford PM, Kean WF, Kraag GR, Gerecz-Simon E, Campbell J. A multicenter study of tenoxicam and diclofenac in patients with osteoarthritis of the knee. *J Rheumatol* 1993; **20**: 999-1004
47 Ehrich EW, Schnitzer TJ, McIlwain H, Levy R, Wolfe F, Weisman M, Zeng Q, Morrison B, Bolognese J, Seidenberg B, Gertz BJ. Effect of specific COX-2 inhibition in osteoarthritis of the knee: a 6 week double blind, placebo controlled pilot study of rofecoxib. Rofecoxib Osteoarthritis Pilot Study Group. *J Rheumatol* 1999; **26**: 2438-2447
48 Nakhostin-Roohi B, Barmaki S, Khoshkhahesh F, Bohlooli S. Effect of chronic supplementation with methylsulfonylmethane on oxidative stress following acute exercise in untrained healthy men. *J Pharm Pharmacol* 2011; **63(10)**: 1290-1294
49 Monfort J, Pelletier J-P, Garcia-Giralt N, Martel-Pelletier J. Biochemical basis of the effect of chondroitin sulfate on osteoarthritis articular tissues. *Ann Rheum Dis* 2007; doi:10.1136/ard.2006.068882
50 Jomphe C, Gabriac M, Hale TM, Heroux L, Trudeau LE, Deblois D, Montell E, Verges J, du Souich P. Chondroitin Sulfate Inhibits the Nuclear Translocation of Nuclear Factor-kappaB in Interleukin-1beta-Stimulated Chondrocytes. *Basic Clin Pharmacol Toxicol* 2007 Nov 5

Peer reviewers: Tetsuya Shinozaki, MD, PhD, Department of Orthopedic Surgery, Maki Hospital, 71-1 Tsukunawa, Takasaki, 370-0075, Japan; Jun Bao, MD, PhD, Associate professor, Department of Pediatrics, Director, Division of Pediatric Rheumatology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, 1665 Kongjiang Road, Shanghai 200092, China; Janette Furuzawa-Carballeda, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Department of Immunology and Rheumatology, Vasco de Quiroga No. 15, Col. Sección XVI, CP 14000, Mexico City, Mexico.